I. THE SYNTHESIS OF TETRAHYDROCANNABINOL HOMOLOGS WITH MARIHUANA ACTIVITY

II. THE STRUCTURE OF RIDDELLIINE

BY

CHARLES FRANK JELINEK

B. S., Montana State College, 1938

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SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY IN THE GRADUATE SCHOOL OF THE UNIVERSITY OF ILLINOIS, 1944

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I. THE SYNTHESIS OF TETRAHYDROCANNABINOL HOMOLOGS WITH MARIHUANA ACTIVITY

Introduction

Cannabinol[1] and cannabidiol,[2] both isolated from "red oil", the physiologically active high-boiling fraction from the vacuum distillation of hemp extracts, were found to possess no marihuana activity. However, it was found that cannabidiol could be isomerized through the influence of acidic reagents to two different physiologically active optical isomers, α-tetrahydrocannabinol and β-tetrahydrocannabinol.[3] Later, a synthetic physiologically active tetrahydrocannabinol (I), isomeric with the α- and β-tetrahydrocannabinols, was prepared.[4] This led to the preparation of homologs of synthetic tetrahydrocannabinol (I) to determine the influence of structure on marihuana activity.

Experimental and Discussion

The syntheses of the *n*-butyl and *n*-hexyl (II) homologs of the *n*-amyl isomer (I) were carried out by the method used for the preparation of the latter.[4] These homologs are 1-hydroxy-3-*n*-alkyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyrans. In addition, 3,5-dimethoxyphenyl ethyl ketone was prepared for use in the synthesis of the *n*-propyl homolog.

The *n*-hexyl homolog (II) was found to be the most active of the series of homologs ranging from methyl to *n*-octyl when tested for marihuana potency.[5] This homolog is almost twice as potent as the *n*-amyl (I) and is more active than the "purified red oil" from hemp extracts. As a consequence, it may find medicinal use, since it possesses a uniform potency, while great variations in physiological activity exist in different samples of marihuana.

A study of Diels-Alder additions to coumarin was instituted to determine whether or not this type of reaction could be used for the synthesis of tetrahydrocannabinols. Attempts to add either butadiene or 2,3-dimethyl-1,3-butadiene to coumarin were unsuccessful. Subsequently, the latter addition was accomplished,[6] and the Diels-Alder addition of isoprene to a substituted

cinnamic acid has been effected to give an intermediate for the possible synthesis of an optically active tetrahydrocannabinol.[7]

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II. THE STRUCTURE OF RIDDELLIINE

Introduction

Feeding experiments with *Senecio riddellii* have shown that its ingestion causes the "walking disease" of horses and cattle in northwestern Nebraska.[1] The active ingredient, riddelliine, had been isolated from *Senecio riddellii*, and its molecular formula was reported as $C_{18}H_{23}O_6N$.[2] This investigation was begun to ascertain further the chemical nature of riddelliine.

Experimental and Discussion

Analysis of riddelliine (I) and of its methiodide definitely established its molecular formula as $C_{18}H_{23}O_6N$. On alkaline hydrolysis, one mole of riddelliine combined with two moles of water to yield the base, retronecine (II), and an acid, $C_{10}H_{14}O_6$, designated as riddellic acid (III).[3]

Direct titration showed the acid (III) to be dibasic, and addition of excess alkali followed by back titration indicated the probable presence of a lactone linkage. Evidence from hydrogenation[3] and polarographic studies[4] showed that the acid (III) has two reducible groups.

Riddelliine absorbed two moles of hydrogen in the presence of Raney nickel to give an amino acid (IV) which was hydrolyzed to yield the base, retronecanol (V) and the acid (III). Riddelliine thus appears to be a cyclic diester which can be hydrogenolyzed in the presence of Raney nickel to yield the amino acid (IV).

With platinum oxide as a catalyst, four moles of hydrogen were absorbed under two to three atmospheres pressure to yield a product which on hydrolysis gave the base (V) and an acid. Under atmospheric pressure, riddelliine absorbed three moles of hydrogen in the presence of platinum oxide.

Riddelliine has thus been shown to be a cyclic diester of the base (II) and the acid (III), each of which is capable of absorbing two moles of hydrogen under two to three atmospheres pressure in the presence of platinum oxide catalyst.

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Vita

The author was born in Miles City, Montana, on February 6, 1917. He attended the elementary schools in that city and was graduated from Custer County High School, Miles City, Montana, in May, 1933. He attended Montana State College from September, 1934, until June, 1938, where he received the degree of Bachelor of Science. From October, 1938, to June, 1940, he was a Rhodes Scholar at the University of Oxford, where he received the degree of Bachelor of Science in Organic Chemistry. He attended the University of Illinois as the New York Community Trust Fellow from September, 1940, to January, 1942. He was a Special Research Assistant in Chemistry from January to June, 1942, when he was called into the Chemical Warfare Service.

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